EXHIBIT C

Robbins PATHOLOGIC BASIS OF DISEASE

5th Edition

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mal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change."[2] To this characterization we might add that the abnormal mass is purposeless, preys on the host, and is virtually autonomous. It preys on the host insofar as the growth of the neoplastic tissue competes with normal cells and tissues for energy supplies and nutritional substrate. Inasmuch as these masses may flourish in a patient who is wasting away, they are to a degree autonomous. Later it becomes evident that such autonomy is not complete. All neoplasms ultimately depend on the host for their nutrition and vascular supply; many forms of neoplasia require endocrine support.

Figure 7–1. Papilloma of the colon with finger-like projections into the lumen. (Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas.)

NOMENCLATURE

All tumors, benign and malignant, have two basic components: (1) proliferating neoplastic cells that constitute their *parenchyma* and (2) *supportive stroma* made up of connective tissue and blood vessels. Although parenchymal cells represent the proliferating "cutting edge" of neoplasms and so determine their nature, the growth and evolution of neoplasms are critically dependent on their stroma. An adequate stromal blood supply is requisite, and the stromal connective tissue provides the framework for the parenchyma. In some tumors, the stromal support is scant, and so the neoplasm is soft and fleshy. Sometimes the parenchymal cells stimulate the formation of an abundant collagenous stroma—referred to as *desmoplasia*. Some tumors, for example some cancers of the female breast, are stony hard or scirrhous. The nomenclature of tumors is, however, based on the parenchymal component.

BENIGN TUMORS. In general, these are designated by attaching the suffix "-oma" to the cell of origin. Tumors of mesenchymal cells generally follow this rule. For example, a benign tumor arising from fibroblastic cells is called a *fibroma*. A cartilaginous tumor is a *chondroma*, and a tumor of osteoblasts is an *osteoma*. In contrast, nomenclature of benign epithelial tumors is more complex. They are variously classified, some based on their cells of origin, others on microscopic architecture, and still others on their macroscopic patterns.

Adenoma is the term applied to the benign epithelial neoplasm that forms glandular patterns as well as to the tumors derived from glands but not necessarily reproducing glandular patterns. On this basis, a benign epithelial neoplasm that arises from renal tubular cells growing in the form of numerous tightly clustered small glands would be termed an adenoma, as would a heterogeneous mass of adrenal cortical cells growing in no distinctive pattern. Benign epithelial neoplasms producing microscopically or macroscopically visible finger-like or warty projections from epithelial surfaces are referred to as *papillomas* (Fig. 7–1). Those that form large cystic masses, as in the ovary, are referred to as *cystadenomas*. Some tumors produce papillary patterns that protrude into cystic spaces and are called *papillary cystadenomas*. When a neoplasm, benign or malignant, produces a macroscopically visible projection above a *mucosal* surface and projects, for example, into the gastric or colonic lumen, it is termed a *polyp*. The term polyp preferably is restricted to benign tumors. Malignant polyps are better designated polypoid cancers.

MALIGNANT TUMORS. The nomenclature of malignant tumors essentially follows the same schema used for benign neoplasms, with certain additions. *Malignant tumors arising in mesenchymal tissue are usually called sarcomas* (Greek "sar" = fleshy) because they have little connective tissue stroma and so are fleshy, e.g., fibrosarcoma, liposarcoma, and leiomyosarcoma for smooth muscle cancer and rhabdomyosarcoma for a cancer that differentiates toward striated muscle. *Malignant neoplasms of epithelial cell origin, derived from any of the three germ layers, are called carcinomas.* Thus cancer arising in the epidermis of ectodermal origin is a carcinoma, as is a cancer arising in the mesodermally derived cells of the renal tubules and the endodermally derived cells of the lining of the gastrointestinal tract. Carcinomas may be further qualified. One with a glandular growth pattern microscopically is termed an *adenocarcinoma*, and one producing recognizable squamous cells arising in any epithelium of the body would be termed a

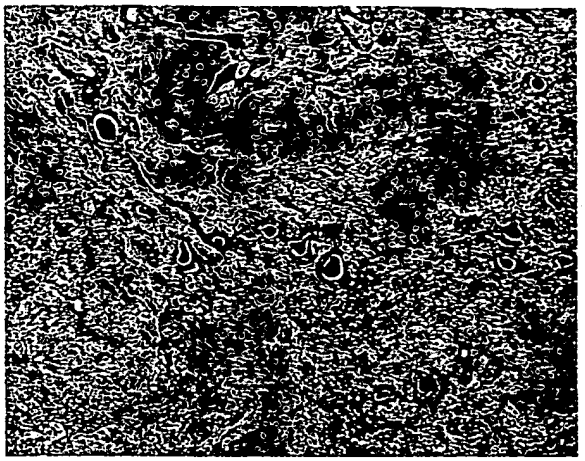

Figure 7–2. Mixed tumor of the parotid gland contains epithelial cells forming ducts and myxoid stroma that resembles cartilage. (Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas.)

Figure 7–3. Teratoma. Three distinct types of adult tissues are seen: a circular island of darkly stained cartilage (mesodermal) in the upper left, a large nest of stratified squamous epithelial cells (ectodermal) on the right, and in the center a gland space lined by columnar cells resembling intestinal tract mucosa (endodermal) *(arrow)*.

squamous cell carcinoma. It is further common practice to specify, when possible, the organ of origin, e.g., a renal cell adenocarcinoma or bronchogenic squamous cell carcinoma. Not infrequently, however, a cancer is composed of undifferentiated cells and must be designated merely as a poorly differentiated or undifferentiated malignant tumor.

In most neoplasms, benign and malignant, the parenchymal cells bear a close resemblance to each other, as though all were derived from a single cell, as indeed we know to be the case with most cancers. Infrequently divergent differentiation of a single line of parenchymal cells creates what are called *mixed tumors*. The best example is the *mixed tumor of salivary gland origin*. These tumors contain epithelial components scattered within a myxoid stroma that sometimes contains islands of apparent cartilage or even bone (Fig. 7–2). All these elements, it is believed, arise from epithelial and myoepithelial cells of salivary gland origin; thus the preferred designation of these neoplasms is *pleomorphic adenoma*. This schizophrenic morphology presumably reflects variable expression of several programs of differentiation that are repressed in the genome of all cells. The great majority of neoplasms, even mixed tumors, are composed of cells representative of a single germ layer. The *teratoma*, in contrast, is made up of a variety of parenchymal cell types representative of more than one germ layer, usually all three. They arise from totipotential cells and so are principally encountered in the gonads but rarely in sequestered primitive cell rests elsewhere. These totipotential cells differentiate along various germ lines, producing, for example, tissues that can be identified as skin, muscle, fat, gut epithelium, tooth structures, and, indeed, any tissue of the body (Fig. 7–3). A particularly common pattern is seen in the ovarian *cystic teratoma* (dermoid cyst), which differentiates principally along ectodermal lines to create a cystic tumor lined by skin replete with hair, sebaceous glands, and tooth structures.

The nomenclature of the more common forms of neoplasia is presented in Table 7–1. It is evident from this compilation that there are some inappropriate but deeply entrenched usages. For generations, carcinomas of melanocytes have been called "melanomas," although correctly they should be referred to as melanocarcinomas. Analogously carcinomas of testicular origin are stubbornly called "seminomas." Other instances will be encountered in which innocent designations belie ugly behavior. Irrational as such usage may be, it is probably more irrational to expect humans to be rational. The converse is also true when ominous terms are applied to usually trivial lesions. An ectopic rest of normal tissue is sometimes called a *choristoma* — as, for example, a rest of adrenal cells